Genetic Variation in the Transcriptomic Response to Low Dose Radiation In Vivo

Brynn H. Voy[1], Lisa Branstetter[1], Arnold Saxton[2] and Michael A. Langston[3]

[1]Life Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6445
[2]Department of Animal Science, University of Tennessee, Knoxville, TN 37996
[3] Department of Computer Science, University of Tennessee, Knoxville, TN 37996

Genetic background influences an individual's response to biological stimuli and is thought to impact the consequences of exposure to ionizing radiation (IR). We used genome-scale gene expression profiling as a tool to characterize the *in vivo* response to IR across multiple inbred strains of laboratory mice, which differ from each other genetically in a way that parallels the differences between human populations. Six common inbred strains of mice – C57Bl6 (B6), DBA/2, A/J, BALB/c, B6.C and C3H/HeJ – were exposed to 10 cGy or 200 cGy dose of a broad-spectrum x-ray flux produced by a standard bremsstrahlung source (maximum voltage = 250 kVp, maximum current = 10 mA, filter = 0.2 mm Cu), and dorsal skin, spleen, thymus and testis were harvested either 1 or 3.5 hours after exposure. Here we have focused on the 10 cGy dose and on spleen collected after 3.5 hours. For this project a specific strain or tissue response to radiation is defined solely by changes in gene expression, based on microarray profiling of ~ 21,000 mouse genes. Data were analyzed using mixed models to test for main effects of radiation alone and to identify genes for which the response to radiation depended on genetic background. Q-values were used to control the false discovery rate. Of the ~ 21,547 genes assayed for expression, accepting a false discovery rate of 5 % and including only genes with observations meeting array data quality criteria in all six strains of mice, a total of 510 genes were significantly responsive to 10 cGy of radiation, regardless of genetic background. Approximately 65% of the genes exhibited increased expression levels. Functional enrichment analysis using Gene Ontology (GO) indicated that genes upregulated in response to low dose radiation were enriched in several GO terms related to immune function and signal transduction. Genes related to cellular energy metabolism and transcriptional regulation were significantly overrepresented among downregulated genes. A number of genes responded to low dose radiation in a manner that varied significantly between strains of mice. The strain-specific responses suggest that immunological consequences, in particular, of low dose exposure are highly dependent upon genetic background. These data may have important implications for genetic susceptibility to radiation outcomes that involve the immune system, or to radiation-induced carcinogenesis. The clearly demonstrate that genetic variability must be taken into account when defining the consequences of low dose exposure.

In parallel to differential expression analysis, we developed a computational approach based on graph theoretical algorithms to extract the potential gene networks that mediate the response to low dose radiation. This method (described in detail in the companion abstract by Langston et al) builds on the tenet that genes in common pathways are more likely to be co-expressed than genes with unrelated functions (i.e., guilt-by-association). Using this approach we identified a number of poorly annotated genes for which there is compelling evidence of an important role in the radiation response. We also identified networks of genes that responded to low dose radiation and that potentially control the outcome of low dose exposure in spleen. Detailed results of both differential expression and network analyses will be presented.